



4164-01-P

## DEPARTMENT OF HEALTH AND HUMAN SERVICES

### Food and Drug Administration

[Docket No. FDA-2012-N-0143]

### Harmful and Potentially Harmful Constituents in Tobacco Products; Established List; Proposed Additions; Request for Comments

**AGENCY:** Food and Drug Administration, HHS

**ACTION:** Notice; request for comments.

**SUMMARY:** The Food and Drug Administration (FDA or the Agency) is requesting comments, including scientific and other information, concerning whether additional harmful and potentially harmful constituents (HPHCs) in tobacco products and tobacco smoke should be added to the Agency's list of HPHCs (the HPHC established list). This information will assist the Agency in determining whether any or all of the 19 constituents listed in this document should be added to the HPHC established list.

**DATES:** Submit either electronic or written comments by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

**ADDRESSES:** You may submit comments as follows:

#### *Electronic Submissions*

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <https://www.regulations.gov>. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to <https://www.regulations.gov> will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring

that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on <https://www.regulations.gov>.

- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

#### *Written/Paper Submissions*

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

*Instructions:* All submissions received must include the Docket No. FDA-2012-N-0143 for "Harmful and Potentially Harmful Constituents in Tobacco Products; Established List; Proposed Additions; Request for Comments." Received comments will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at <https://www.regulations.gov> or at the Dockets Management Staff Office between 9 a.m. and 4 p.m., Monday through Friday.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states “THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION.” The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on <https://www.regulations.gov>. Submit both copies to Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as “confidential.” Any information marked as “confidential” will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA’s posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at:  
  
<https://www.fda.gov/regulatoryinformation/dockets/default.htm>.

*Docket:* For access to the docket to read background documents or the electronic and written/paper comments received, go to <https://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the “Search” box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:** Eric Mandle or Nathan Mease, Center for Tobacco Products, Food and Drug Administration, Document Control Center, Bldg. 71, Rm. G335, 10903 New Hampshire Ave., Silver Spring, MD 20993-0002; 1-877-287-1373, CTPRegulations@fda.hhs.gov.

**SUPPLEMENTARY INFORMATION:**

I. Background

The Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act), enacted on June 22, 2009, amends the Federal Food, Drug, and Cosmetic Act (FD&C Act) by, among other things, adding a new chapter (chapter IX) granting FDA the authority to regulate the manufacture, marketing, and distribution of tobacco products to protect the public health generally and to reduce tobacco use by minors (Pub. L. 111–31). Cigarettes, cigarette tobacco, roll-your-own (RYO) tobacco, and smokeless tobacco were immediately subject to chapter IX.

For other kinds of tobacco products, the statute authorizes FDA to issue regulations “deeming” them to be subject to chapter IX. FDA published a final rule on May 10, 2016 (81 FR 28974) (the Deeming Rule), deeming all products that meet the statutory definition of “tobacco product” set forth in section 201(rr) of the FD&C Act (21 U.S.C. 321(rr)), including components and parts, but excluding accessories of deemed products, to be subject to chapter IX of the FD&C Act.<sup>1</sup>

Section 904(e) of the FD&C Act (21 U.S.C. 387d(e)) requires FDA to establish, and periodically revise as appropriate, “a list of harmful and potentially harmful constituents, including smoke constituents, to health in each tobacco product by brand and by quantity in each

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<sup>1</sup> This final rule, “Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act,” 21 CFR part 1100, is available at <https://www.gpo.gov/fdysys/pkg/FR-2016-05-10/pdf/2016-10685.pdf>.

brand and subbrand.” FDA first established the list on April 3, 2012 (77 FR 20034) (the April 2012 notice).<sup>2</sup> The list currently contains 93 HPHCs (the HPHC established list). The April 2012 notice describes the history of the HPHC established list, and for additional background, we refer readers to that notice and the notice FDA published in the *Federal Register* on August 12, 2011 (76 FR 50226) (the August 2011 notice), in which we solicited public comment, including scientific and other information, concerning the HPHCs in tobacco products and tobacco smoke, including which constituents should be included on the HPHC established list, and the criteria used in determining whether a constituent is harmful or potentially harmful such that it should be included on the HPHC list.<sup>3</sup>

## II. Proposed Changes to the HPHC List

### *A. Application of Existing Criteria to Deemed Products; Proposed Addition of Glycidol and Ethylene Glycol to the HPHC List*

As discussed previously, when the Agency established the HPHC established list, the tobacco products that were subject to its authorities under chapter IX of the FD&C Act were limited to cigarettes, cigarette tobacco, RYO tobacco, and smokeless tobacco products. Since then, however, the FDA’s tobacco product authorities were extended under the Deeming Rule to all products, including components and parts (but excluding accessories of deemed products) that meet the statutory definition of tobacco product, including electronic nicotine delivery systems (ENDS). Therefore, consistent with section 904(e) of the FD&C Act, the Agency is considering revising the HPHC established list to reflect the current range of tobacco products now subject to

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<sup>2</sup> “Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List,” 77 FR 20034 (April 3, 2012).

<sup>3</sup> “Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Request for Comments,” 76 FR 50226 (August 12, 2011). The August 2011 notice and the April 2012 notice are collectively referred to as the *Federal Register* notices.

the Agency's tobacco product authorities as well as the Agency's growing scientific expertise with respect to all tobacco products.

## 1. Glycidol

FDA has tentatively concluded that in revising the HPHC established list, the Agency should continue to apply the criteria that were originally applied when determining whether a constituent should be put on the list. Glycidol is a thermal byproduct of glycerol, a common component in e-liquids. In other words, glycidol can form and appear in the aerosol when a glycerol-containing solvent such as an e-liquid is heated and aerosol is produced (Refs. 1-2). Following a review of the data concerning degradation of glycerol, FDA has applied the original criteria and tentatively concluded that glycidol should be included on the HPHC established list, unless other scientific information obtained by or submitted to the Agency shows that the constituent is not, in fact, harmful or potentially harmful. The International Agency for Research on Cancer (IARC) has identified glycidol as a probable carcinogen (Ref. 3). As discussed in the April 2012 notice, FDA has concluded that it should consider a constituent meeting this criterion to be harmful or potentially harmful, such that it should be included on the HPHC established list, unless other scientific information obtained by or submitted to the Agency shows that the constituent is not, in fact, harmful or potentially harmful.<sup>4</sup>

## 2. Ethylene Glycol

In accordance with the original criteria, FDA has tentatively concluded that ethylene glycol should also be included on the HPHC established list, unless other scientific information obtained by or submitted to the Agency shows that the constituent is not, in fact, harmful or potentially harmful. In 2015, the California Environmental Protection Agency identified

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<sup>4</sup> For more information, we refer you to the April 2012 notice.

ethylene glycol (ingested) as a reproductive toxicant based on its developmental toxicity (Ref. 4).<sup>5</sup> As discussed in the April 2012 notice, FDA has concluded that it should consider a constituent meeting this criterion to be harmful or potentially harmful, such that it should be included on the HPHC established list, unless other scientific information obtained by or submitted to the Agency shows that the constituent is not, in fact, harmful or potentially harmful. Ethylene glycol has been identified in e-liquids, indicating that this compound may be used to replace glycerol and propylene glycol (Refs. 5 and 6).<sup>6</sup>

*B. Addition of a Criterion for Identifying Constituents that Cause or Have the Potential to Cause Harm*

Furthermore, at this time, FDA has tentatively concluded that the Agency should apply one additional criterion when determining whether a constituent should be included on the HPHC established list. Specifically, FDA tentatively concludes that in addition to the previously described criteria, the following criterion also should be applied for determining whether a constituent should be included on the HPHC established list, unless other scientific information obtained by or submitted to the Agency shows that the constituent is not, in fact, harmful or potentially harmful:

- Constituents identified by the National Institute for Occupational Safety and Health (NIOSH) as having adverse respiratory effects.

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<sup>5</sup> Users of tobacco products can be exposed to ethylene glycol through ingestion as well as other routes of administration. For example, during use of inhaled products, a fraction of the aerosol is deposited in the mouth-throat area and is swallowed, resulting in subsequent systemic exposures to aerosol constituents via the oral route. In June 2015, ethylene glycol was added to the list of chemicals known to the State of California to cause reproductive toxicity under Proposition 65, or the Safe Drinking Water and Toxic Enforcement Act of 1986, Health and Safety Code section 25249.5 et seq. See <https://oehha.ca.gov/proposition-65/cmr/ethylene-glycol-ingested-listed-reproductive-toxicant> (accessed October 2018).

<sup>6</sup> The Agency has expressed concern about ethylene glycol in e-liquid tobacco products before. See the Deeming Rule (81 FR 28974 at 29029).

FDA believes that having the additional criterion described in this document for use in determining whether a constituent is harmful or potentially harmful will be beneficial. We have tentatively identified 17 constituents that meet this criterion. They are: acetic acid, acetoin, acetyl propionyl, benzyl acetate, butyraldehyde, diacetyl, ethyl acetate, ethyl acetoacetate, ethylene glycol (as discussed in section II.A., this compound also meets one of the criteria that were originally applied), furfural, glycerol, isoamyl acetate, isobutyl acetate, methyl acetate, n-butanol, propionic acid, and propylene glycol. As part of the Centers for Disease Control and Prevention (CDC), NIOSH is the Federal agency responsible for conducting research and making science-based recommendations to prevent work-related illness and injuries, including those related to human health hazards and respiratory disease from inhalation exposures to toxicants. In reaching the tentative conclusion described above, the Agency notes that FDA already considers whether NIOSH has identified a constituent as a potential occupational carcinogen in determining whether that constituent should be included on the HPHC list.<sup>7</sup>

### *C. Proposed Addition of Diethylene Glycol to the HPHC List*

FDA has proposed diethylene glycol (DEG) as an HPHC because we are concerned that a product that contains either glycerol or propylene glycol also could be contaminated, perhaps inadvertently, by DEG. The acute health consequences from exposure to DEG-contaminated products may be serious and irreversible (Ref. 7). Poisoning because of DEG is not a common occurrence. Most of the documented cases of illness and death from DEG poisoning have been outbreaks where DEG was substituted in pharmaceutical preparations for the glycols or glycerine

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<sup>7</sup> See the April 2012 notice (77 FR 20034 at 20035). In this notice, FDA concluded that it should adopt the criteria proposed in the August 2011 notice.



constituents customarily used (Ref. 8). Toxicity can result from ingestion<sup>8</sup> or dermal exposure to DEG-contaminated products (Refs. 9-10). Inhalation exposure to DEG-contaminated products also can have serious health consequences (Refs. 11 and 12). Suppliers of glycerol and propylene glycol can dilute them with DEG (Refs. 13 and 14) and manufacturers, unaware of the added DEG, can use the contaminated glycerol or propylene glycol in tobacco products. Although FDA has no reason to believe that U.S. suppliers of glycerol and propylene glycol currently use DEG, FDA has detected DEG in e-liquids and ENDS aerosol (Refs. 15 and 16).<sup>9</sup> Therefore, the Agency has tentatively concluded that DEG should be included on the HPHC established list.

#### *D. Proposed Addition of 19 Toxicants to the HPHC List*

Applying all the criteria discussed earlier in this document and using available information, FDA tentatively concludes that the 19 toxicants in table 1 should be added to the HPHC established list. This tentative conclusion is consistent with our definition of “harmful and potentially harmful constituent” as set forth in the Agency guidance entitled “Harmful and Potentially Harmful Constituents’ in Tobacco Products as Used in Section 904(e) of the Federal Food, Drug, and Cosmetic Act” (Revised) dated August 2016 (the HPHC Guidance) in that the Agency has reviewed data regarding constituents identified in tobacco products and their smoke, including in e-liquids and in aerosols of ENDS products that are, or potentially are, inhaled, ingested, or absorbed into the body, including as an aerosol (vapor) or any other emission.

Table 1--List of the Additional Chemicals and Chemical Compounds Identified by FDA as Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke

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<sup>8</sup> For more information on DEG, including a discussion of ingestion toxicity, we refer you to FDA’s guidance for industry *Testing of Glycerin for Diethylene Glycol* (available at <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm070347.pdf>).

<sup>9</sup> The Agency has expressed concern about DEG in tobacco products before. See the Deeming Rule (81 FR 28974 at 29031) and the proposed deeming rule (79 FR 23141 at 23157).

Constituent	Carcinogen (CA), Respiratory Toxicant (RT), Reproductive or Developmental Toxicant (RDT), Poisonous Chemical (PC)
Acetic Acid	RT
Acetoin (also known as 3-hydroxy-2-butanon3	RT
Acetyl propionyl (also known as 2,3-pentanedione)	RT
Benzyl acetate	RT
Butyraldehyde	RT
Diacetyl	RT
Diethylene glycol	PC
Ethyl Acetate	RT
Ethyl Acetoacetate	RT
Ethylene Glycol	RT, RDT
Furfural	RT
Glycerol	RT
Glycidol	CA
Isoamyl Acetate	RT
Isobutyl Acetate	RT
Methyl Acetate	RT
n-Butanol	RT
Propionic Acid	RT
Propylene Glycol	RT

### III. Identification of HPHCs Is an Ongoing Effort

FDA recognizes that there may be constituents that are “harmful or potentially harmful” that FDA neither included on the established HPHC list nor proposed to be added to that list per table 1. The criteria described previously in the April 2012 notice and the additional criterion described in this document generally depend on a chemical or chemical compound being studied and identified by FDA or another regulatory entity as having adverse effects that are relevant to cancer, cardiovascular, respiratory, developmental, or reproductive effects. That a constituent has not been so identified by FDA or other entities could be because it has not been adequately studied or has not yet been systematically reviewed. Consistent with our obligations under section 904(e) of the FD&C Act, FDA intends to continue:

- Our efforts to review other disease outcomes to assess whether additional chemicals or chemical compounds in tobacco products or tobacco smoke, including chemicals or

chemical compounds in the emissions from the range of tobacco products now deemed to be subject to chapter IX of the FD&C Act, are harmful or potentially harmful constituents that contribute to the risk of other diseases;

- Our consideration of whether additional or different criteria should be selected to help identify other classes of harmful or potentially harmful chemicals and chemical compounds for inclusion on the HPHC established list and whether individual constituents should be added; and
- Our efforts to review new information to determine if it would be appropriate to remove one or more of the constituents that appear on the HPHC established list, or to add additional constituents to the list.

#### IV. Request for Comments and Information

FDA is soliciting public comment on this notice, including scientific and other information on the following topics:

- The additional criterion FDA is proposing to use when determining whether a constituent should be added to the HPHC established list;
- Whether any chemicals or chemical compounds not listed in table 1 should be included because they are harmful or potentially harmful, including supporting scientific or other information; and
- Whether any of the chemicals or chemical compounds listed in table 1, including as a result of the proposed criterion, should not be included because they are not harmful or potentially harmful, including supporting scientific or other information.

Interested persons may submit to the Dockets Management Staff (see ADDRESSES) either electronic or written comments regarding this document.

## V. References

The following references marked with an asterisk (\*) are on display at the Dockets Management Staff (see ADDRESSES) and are available for viewing by interested persons between 9 a.m. and 4 p.m., Monday through Friday; they also are available electronically at <https://www.regulations.gov>. References without asterisks are not on public display at <https://www.regulations.gov> because they have copyright restriction. Some may be available at the website address, if listed. References without asterisks are available for viewing only at the Dockets Management Staff. FDA has verified the website addresses, as of the date this document publishes in the *Federal Register*, but websites are subject to change over time.

1. Laino, T., C. Tuma, A. Curioni, et al., “A Revisited Picture of the Mechanism of Glycerol Dehydration,” *Journal of Physical Chemistry A*, 115(15):3592–3595, 2011.

<https://doi.org/10.1021/jp201078e>.

2. Sleiman, M., J. Logue, V. Montesinos, et al., “Emissions from Electronic Cigarettes: Key Parameters Affecting the Release of Harmful Chemicals,” *Environmental Science & Technology*, (50)9644-9651, 2016. <https://doi.org/10.1021/acs.est.6b01741>.

3. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 77, at 482 (2000). <https://monographs.iarc.fr/wp-content/uploads/2018/06/mono77.pdf>.

\*4. Borghardt, J. M., C. Kloft, and A. Sharma, “Inhaled Therapy in Respiratory Disease: The Complex Interplay of Pulmonary Kinetic Processes,” *Canadian Respiratory Journal*, 2018, doi:10.1155/2018/2732017. <http://downloads.hindawi.com/journals/crj/2018/2732017.pdf>.

5. Dionex Corporation, “Determination of Ethylene Glycol and Diethylene Glycol in a Sorbitol Solution,” Application Note 246, LPN 2505, Sunnyvale, CA, 2016.

<https://assets.thermofisher.com/TFS-Assets/CMD/Application-Notes/AN-246-IC-Ethylene-Diethylene-Glycol-Sorbitol-LPN2505-EN.pdf>.

6. Hutzler, C., M. Paschke, S. Kruschinski, et al., “Chemical Hazards Present in Liquids and Vapors of Electronic Cigarettes,” *Archives of Toxicology*, 88(7): 1295-1308, 2014.  
<https://doi.org/10.1007/s00204-014-1294-7>.

7. Diethylene Glycol Poisoning (Cal. Poison Control System) Dec. 21, 2012, available at <https://calpoison.org/news/diethylene-glycol-poisoning> (last accessed on October 10, 2018).

8. Schep, L. J., R. J. Slaughter, W. A. Temple, and D. M. Beasley, “Diethylene Glycol Poisoning” *Clinical Toxicology*, 47(6):525–535 at 526, 2009.  
<https://doi.org/10.1080/15563650903086444>.

9. Devoti, E., E. Marta; E. Belotti, et al., “Diethylene Glycol Poisoning from Transcutaneous Absorption,” *American Journal of Kidney Diseases*, 65(4):603-606, 2015.  
<https://doi.org/10.1053/j.ajkd.2014.07.032>.

\*10. National Industrial Chemicals Notification and Assessment Scheme, Existing Hazard Assessment Report, Diethylene Glycol (DEG), Australian Government Department of Health and Ageing (June 2009).  
[https://www.nicnas.gov.au/\\_\\_data/assets/word\\_doc/0018/37323/Diethylene-glycol-DEG-hazard-assessment.docx](https://www.nicnas.gov.au/__data/assets/word_doc/0018/37323/Diethylene-glycol-DEG-hazard-assessment.docx).

\*11. Health Council of the Netherlands. “Diethylene glycol; Health-based recommended occupational exposure limit.” <https://www.healthcouncil.nl/documents/advisory-reports/2007/10/17/diethylene-glycol>.

12. Sanina Y., “Remote Consequences of Chronic Inhalation of Diethylene Glycol,” *Gigiena I Sanitariia* (1968).

\*13. FDA Guidance for Industry, “Testing of Glycerin for Diethylene Glycol,” May 2007, available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/testing-glycerin-diethylene-glycol>.

\*14. August 2, 1996, CDC Morbidity and Mortality Weekly Report.  
<https://www.cdc.gov/mmwr/PDF/wk/mm4530.pdf>.

\*15. Varlet, V. et al., “Toxicity Assessment of Refill Liquids for Electronic Cigarettes,” *International Journal of Environmental Research and Public Health* 2015, 12, 4796-4815.  
<https://www.mdpi.com/1660-4601/12/5/4796>.

\*16. FDA Memorandum, “Evaluation of E-Cigarettes,” from B. Westenberger, CDER/OPS/OTR, to M. Levy, Center for Drug Evaluation and Research, Office of Compliance, May 4, 2009.

**Dated:** July 30, 2019.

**Lowell J. Schiller,**

*Principal Associate Commissioner for Policy.*

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